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CLINICAL PROCEEDINGS

of the

CHILDREN'S HOSPITAL

WASHINGTON, D. C.

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October 1952

VOLUME VIII NUMBER 10

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CLINICAL PROCEEDINGS

OF THE CHILDRENS HOSPITAL

13th and W Streets, Washington 9, D. C.

Vol. VIII *October 1952* No. 10

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CARCINOMA OF THE THYROID IN CHILDREN*

Special Report No. 244

Theodore Winship, M.D.†

Until comparatively recent years thyroid carcinoma was considered to be extremely rare in children; consequently, symptoms of the disease were frequently neglected until curative therapy was difficult or impossible. Patients are still encountered occasionally who, after having sought medical advice concerning a persistent, painless nodule in the thyroid or in the lymphatic drainage area of the thyroid, have been told, "Don't bother it until it bothers you."

In 1899, Ehrhardt reported the case of a seven-year old child who was treated for carcinoma of the thyroid gland. This is apparently the first well-documented case of this disease reported in the pediatric age-group. An extensive review of the 19th and 20th century literature on the thyroid gland reveals 93 reported cases. In addition to these, four cases have been observed at Children's Hospital, Washington, D. C. These are presented in detail.

CASE REPORTS

Case 1: An eight-year old girl was admitted to Children's Hospital, on the service of Dr. H. H. Schoenfeld, because of cervical adenopathy which had been present for three years. Physical examination revealed several painless, enlarged lymph nodes in the right jugular chain. The thyroid gland was not abnormal. The parents gave permission for a biopsy only. The tissue removed was inadequate for a definite diagnosis, but Boeck's sarcoid was suggested. Roentgenograms of the chest revealed a nodular widening of the mediastinal shadow consistent with Boeck's sarcoid. Further investigation and therapy were refused.

Two years and seven months later the child was re-admitted in severe respiratory distress. At this time a hard, nodular mass involving the right lobe of the thyroid was found, extending laterally to include the right sternocleidomastoid muscle and inferiorly to the clavicle. Roentgenograms showed a "snowstorm appearance" in both lungs and a mass compressing the trachea and displacing it to the left. Dyspnea and cyanosis were so marked that an immediate operation was performed. A portion of the mass in the neck was removed to allow an adequate air passage. Six hours after the operation the patient died.

At autopsy, there was a firm, mottled, reddish-gray mass involving the entire right lobe of the thyroid gland, the isthmus, and the medial third of the left lobe. The

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* Abstract of an article published in the "Proceedings of the American Goiter Association; pp. 364–389, 1952.

Aided by a grant from the Research Foundation of Children's Hospital, Washington, D. C.

† Department of Pathology, Children's Hospital, Washington, D. C.

mass extended into the mediastinum, where it partially encircled both the right and left carotid arteries and was densely adherent to the arch of the aorta. The lymph nodes of the right jugular chain were involved by tumor, as were those of the bronchi. Much of the lung tissue was replaced by small, rounded nodules of tumor, except in the apices where the tissue was emphysematous.

Microscopically, the cells formed a well-differentiated, glandular pattern consisting of small acini which contained no colloid. Numerous psammoma bodies were present throughout the primary and metastatic tumor. There was no evidence of a previously existing adenoma, and there was wide invasion of the adjacent tissues. The metastatic carcinoma showed a much greater tendency toward a papillary structure than did the primary tumor.

Diagnosis: Papillary adenocarcinoma.

Case 2: A nine-year old girl was admitted to Children's Hospital, on the service of Dr. C. E. Keegan, for the treatment of a 3-centimeter painless mass in the neck which had been enlarging gradually for seven months. Physical examination showed a hard, non-tender nodule in the region of the medial portion of the right lobe of the thyroid gland. Roentgenograms of the chest revealed no abnormality. At operation, the right lobe of the thyroid and an enlarged, hard, suprasternal nodule were removed. In the right lobe was found a well-circumscribed, unencapsulated, firm, greyish nodule, measuring 3 cm. in its greatest diameter.

Microscopic examination of the thyroid nodule revealed small, uniform, cuboidal cells, forming a closely-packed papillary growth with many small, and a few large, acini containing varying amounts of colloid. The nodule removed from the suprasternal notch contained the same type of tissue.

Diagnosis: Papillary adenocarcinoma.

Four years later, the patient is well but has a 2-centimeter firm, painless node in the suprasternal notch which appears attached to the trachea. This is assumed to be metastatic carcinoma, but it can not be proved, for the parents will not agree to a second operation at this time.

Case 3: A twelve-year old girl was admitted to Children's Hospital, on the service of Dr. R. E. Moran, complaining of a hard mass in her neck. This had been present for more than two years and had been growing rapidly for six months. At operation, a firm mass, involving most of the left lobe of the thyroid gland, was found to be densely adherent to the trachea, and a hemithyroidectomy was performed.

Microscopically, the tissue showed a predominantly papillary pattern with numerous scattered acini, only a few of which contained colloid. Many of the larger acini contained thick papillary infoldings of cells which, in turn, were branched and sometimes filled the acinus.

Diagnosis: Papillary adenocarcinoma.

Six months after the operation, the patient was sent to Memorial Hospital, New York City, where pulmonary metastases were found to be present. A large dose of radioactive iodine was administered for the purpose of destroying the remaining normal thyroid tissue. The patient then received large doses of propylthiouracil in an effort to stimulate the functioning component of the thyroid metastases. Following the accomplishment of this, the metastatic carcinoma was treated with radioactive iodine. Three years after her first admission, the pulmonary metastases are still present, but the patient is reported to be in good health with no evidence of growth abnormality or of hypothyroidism.

Case 4: A nine-year old girl was admitted to another hospital for the removal of a slowly enlarging, painful mass at the angle of the left mandible. At the time of operation an enlarged lymph node found in the opposite side of the neck was removed also. The mass at the angle of the left jaw was diagnosed as a parotid cyst, while the lymph node from the right jugular chain proved to be papillary carcinoma, metastatic from the thyroid gland. The child was transferred to Children's Hospital, on the service of Dr. G. H. McAteer, where a right hemithyroidectomy was performed and several lymph nodes were removed from the right side of the neck.

The right lobe of the thyroid was slightly nodular and moderately enlarged. Cut section showed a retracted, pinkish-gray surface with no evidence of adenomas.

Microscopic examination showed a papillary structure with narrow cystic spaces and very few acini containing small amounts of colloid.

Diagnosis: Papillary adenocarcinoma.

Six months after the operation, the patient is alive and well with no evidence of recurrence or further metastases.

These four cases illustrate many of the characteristic features of childhood thyroid carcinoma. The disease is found predominantly in females. The initial finding is usually a slowly growing, firm, painless mass in the thyroid gland or in the jugular chain of lymph nodes. The histologic type is predominantly papillary and some of the tumors show features which indicate the probability that they would pick up therapeutic amounts of radioactive iodine. If the disease is neglected or inadequately treated, metastases may be expected to appear in the cervical lymph nodes and lungs and death may occur.

In an attempt to discover the incidence of childhood thyroid carcinoma, a survey was conducted. A questionnaire was sent to thirty children's hospitals and to almost five hundred of the larger, approved general hospitals in the United States, Alaska and the Hawaiian Islands. By means of the survey, 95 hitherto unreported cases of childhood thyroid carcinoma were collected. These, in addition to the four patients herein reported and the 93 previously reported, comprise a total of 192 cases in which thyroid carcinoma was diagnosed before the age of fifteen years.

Statistics compiled at Children's Hospital, Washington, D. C., show that approximately 378,000 patients less than fifteen years of age have been treated during the past thirty-six years. During this period, eight children have been observed who had palpable masses in the thyroid gland. Three of these cases proved, on operation, to have multiple benign adenomas, and one had a single benign adenoma. In four patients, the nodularity was caused by carcinoma. Thus, fifty per cent of all clinically nodular goiters in this hospital have been proved to be carcinoma.* Data from other pub-

* A recent report stated, due to a statistical error, that nine discrete thyroid adenomas had been observed at Children's Hospital, Washington, D. C., five of which were carcinoma. A thorough search of the hospital records does not substantiate this report.

lished and unpublished sources show that twenty-nine per cent of one hundred and forty-five non-toxic nodular goiters in children of less than fifteen years of age contained carcinoma. This incidence is considerably higher than the occurrence of carcinoma in nodular goiters in adults and emphasizes the importance of surgical removal of nodular goiters in children.

The first sign of the disease in most of the patients was a painless nodule, either in the region of the thyroid gland, or less often, in the lymphatic drainage area of the gland. In only one case was the disease first manifested by symptoms from distant metastases, as is occasionally seen in adults. Few of the children in this study had hoarseness, dysphagia, dyspnea, or other symptoms of advanced thyroid carcinoma, although six children died post-operatively, indicating that they probably had advanced disease at the time of operation.

The prognosis of children with thyroid carcinoma is not good. The mortality rate for the entire group, followed for an average of only thirty-eight months, was 15.2 per cent, and 20 per cent of all of the cases are either dead or known to be living with disease. Considering the twenty-five children known to be living with disease, the mortality rate in this series at the end of only five years can be estimated to be 20 per cent.

This disease is so uncommon that only by assembling the cases can different methods of therapy be evaluated. It is hoped that the cases included in this report can be followed for fifteen or twenty years, for periodic recheck of patients will disclose early recurrence or metastases which may then be adequately treated. Eventually, if this is done, statistics will be available which may determine the most satisfactory methods of therapy.

Other conditions which can simulate carcinoma of the thyroid gland in children are branchial cleft cyst, tuberculous adenitis, lymphoma, dermoid cyst, thyroglossal duct cyst, and adenitis secondary to an infection in the head or neck area; however, any persistent nodule in a child's neck should suggest carcinoma of the thyroid and no delay should occur in establishing a diagnosis, for the first procedure, if sufficiently radical, offers the best, and possibly the only, chance for a cure in carcinoma of the thyroid in children.

SUMMARY

The literature relative to thyroid carcinoma in children is reviewed. To date, ninety-three cases of this disease have been reported.

Four additional cases of thyroid carcinoma, from Children's Hospital, Washington, D. C., are described in detail.

The results of a survey of more than five hundred large hospitals in the United States, Alaska, and the Hawaiian Islands are presented. Ninety-

five hitherto unreported cases in patients of less than fifteen years of age are summarized.

The clinical and pathological aspects of thyroid carcinoma in children are reviewed.

The incidence of carcinoma in relation to nodular goiter is discussed.

Inadequate follow-up and deficient hospital records were the chief factors limiting the evaluation of therapy.

Because of the high mortality rate in children with thyroid carcinoma, the importance of early diagnosis and prompt and radical removal of all nodular goiters is emphasized.

THE DIAGNOSTIC PROBLEM POSED BY THE COEXISTENCE OF EVENTRATION OF THE RIGHT DIAPHRAGM AND SIMPLE POLYP OF THE COLON

Case Report No. 245

Francis M. Mastrota, M.D.

INTRODUCTION

The single cause for an entire symptom complex is a long standing diagnostic dictum. This is especially true in pediatrics where complexities of pathology rarely exist. Strict adherence to this dictum, however, may considerably delay or obscure the diagnosis when two or more unrelated conditions co-exist. The following case is presented as representative of this fact.

Case Report A. F. 48–11181

A three and one-half year old colored male was admitted to Children's Hospital on April 9, 1952 with the history of passing three dark stools with clots which his mother recognized as blood. He also vomited on one occasion but the vomitus contained no blood.

Past medical history revealed the birth weight to be 4 pounds, 1 ounce. The patient was one of twins. He was immediately breast fed and later maintained on an evaporated milk formula. At the age of four weeks, he was admitted to this hospital. A congenital heart disease was suspected, but no specific type was diagnosed. X-ray of the chest at this admission showed an opacity at the right cardiophrenic angle. This was interpreted as atelectasis and possible hiatal hernia. Barium study of the upper gastrointestinal tract revealed no barium to enter the cardiophrenic opacity. He was discharged with the final diagnosis of congenital heart disease, type undetermined, and atelectasis of the right lower lobe. Five months later he was again readmitted with bronchopneumonia. The previously existing shadow at the cardiophrenic angle was reported to be unchanged. He was discharged after twelve days of

hospitalization. The family history revealed both parents living and well. There was no illness among his six siblings. Any history of contact with tuberculosis was denied.

Physical examination on admission showed the patient to be an alert, three year old colored male who did not appear acutely ill. His head was symmetrical; eyes reacted to light and accommodation; and sclerae were clear. Examination of the ears, nose and throat was normal. The lungs were clear. There was a grade 3 systolic mur-

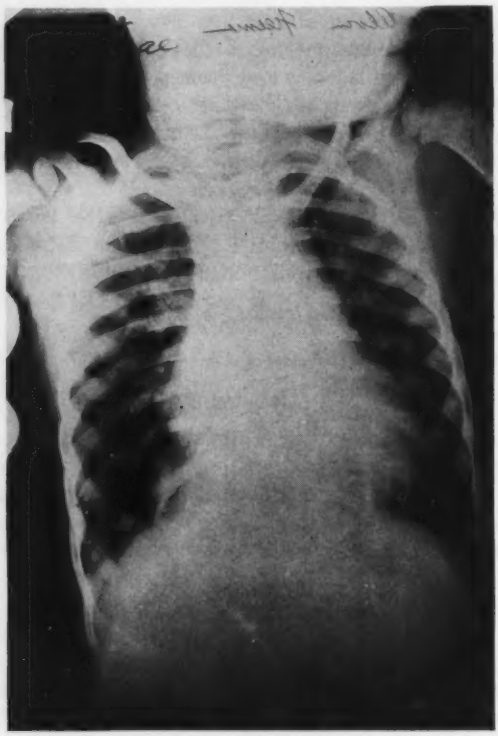

FIG. 1. X-ray of the chest.

mur heard over the precordium, loudest at the apex. The abdomen was soft and there were no masses or organs palpable. There was no tenderness to superficial or deep palpation. The temperature was 99.0°F; pulse, 100; respirations, 20.

Initial hemogram revealed 10.5 grams of hemoglobin; 3,700,000 red blood cells; 9,700 white blood cells with 40 segmented forms, 1 band form and 59 lymphocytes per 100 cells. Platelets were normal. Bleeding time was 1½ minutes. The sedimentation rate was 26 millimeters per hour. Volume of packed corpuscles, 36 volumes per cent. Serological test for syphilis was negative. No sickling of erythrocytes was noted. Three stool cultures were negative for enteric pathogens. Ova and parasites were not found in the stools. Occult blood was 4 plus in the stools. PPD No. 2 was positive.

Roentgenographic examinations included a flat plate of the abdomen and barium enema which revealed no evidence of pathology. Examination of the gastrointestinal tract after ingestion of barium meal showed normal outline and filling of the stomach and intestines. X-rays of the chest showed evidence of bilateral broncohpneumonia and the existence of an opaque mass at the cardiophrenic angle as previously described. Lipiodine bronchogram revealed the trachea to be well outlined. In the right

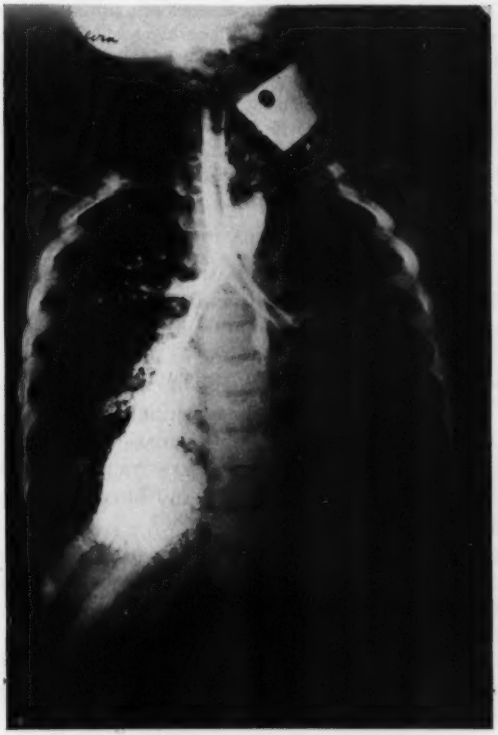

FIG. 2. Lipiodine Bronchogram of the chest.

chest there was a coalescence of an opaque material in the lower right lobe, but there was no connection between the bronchial system and the opacity in the cardiophrenic angle. Bronchoscopic examination showed the right upper and lower lobe bronchi to be normal. The right middle lobe bronchus was not found. Secretions were obtained from the lower lobe and cultured for tuberculous organisms. The culture was found later to be negative. Bronchoscopic examination revealed no pathology that might account for the melena.

Hospital Course: During the first 76 hospital days, the patient was comfortable and afebrile except for two occasions when he had an upper respiratory infection. To establish the diagnosis, underwent two bronchoscopies, one proctoscopic examina-

tion, two barium enemas, three gastrointestinal series, seven x-rays of the chest, two flouroscopic examinations, and one lipiodine bronchogram. Consultations were obtained from the cardiac and general and chest surgical services. The laboratory contributed eleven hemograms, three urinalyses, three stool cultures, twelve stool examinations for occult blood all of which were positive, three sedimentation rates and hematocrits.

On the 77th hospital day an exploratory laparotomy was performed revealing an accessory hepatic lobe on the mid anterior surface of the liver. This was causing an outpouching of the diaphragm but no true diaphragmatic hernia was present. It was the opinion of the surgeon that this was the cause of the peculiar shadow seen at the cardiophrenic angle by x-ray. No surgery was performed on this lobe or on the diaphragm. The bowel was explored from the diaphragm to the rectum, and in the mid portion of the transverse colon, a large friable polyp, measuring two centimeters in diameter, was found. The bowel was opened and the polyp was removed. The patient made an uneventful recovery and was discharged on the eleventh postoperative day having no melena since operation.

DISCUSSION

Operation was delayed since it was the general opinion to diagnose a condition which would cause both rectal bleeding and the mass in the cardiophrenic angle. All possible conditions that might give rise to such a condition were ruled out or were later to be ruled out by laparotomy. In the differential diagnosis may possibilities were considered: such as duplication of the bowel, lung or mediastinal tumor, congenital heart disease, tuberculosis, atelectasis, diaphragmatic hernia with an ulcer, Meckel's diverticulum and intestinal polyp.

Persistent melena with the absence of any bleeding tendency fixed attention to the bowel.

Sometimes melena may be so subtle as to make itself known only by a secondary anemia or the finding of occult blood in the stool by chemical tests. On rare occasions it may be a sudden expulsion of blood that threatens exsanguination. Often a careful history and examination of the type of blood passed with the stool will limit the possible causes of melena. If the blood is bright red it is probably coming from some point low in the bowel such as the sigmoid, rectum or anus. Rectal polyp, foreign body, hemorrhoid, purpura, hemophilia, hemorrhage disease of the newborn and fissure in ano should be considered. Constipation is still probably the most common cause of bright red blood in a child's stool. When the blood is black, it comes from some point high in the gastrointestinal tract or possibly has been swallowed from the respiratory tract. Nose bleeds, gastric or duodenal ulcer, violent vomiting, esophageal varices, purpura, hemophilia, and trauma should be considered.

Blood that is well mixed with stool and is neither tarry black nor bright red probably comes from some midpoint of the gastrointestinal tract. Purpura, trauma, typhoid fever, hemophilia, Meckel's diverticulum, polyp

and intussusception are a few possible causes. A sudden brisk, usually painless hemorrhage strongly points to a bleeding Meckel's diverticulum. Reddish jelly-like fluid often accompanied by colic is found in intussusception. Polyps located higher than the sigmoid colon frequently cause chronic bleeding with blood that is well mixed with the stool.

The cause of fresh blood in the stool can usually be diagnosed by digital and visual examination of the anus and rectum or by investigating for hemorrhage diseases.

Causes of bleeding from the upper and midportions of the gastrointestinal tract are more obscure and diagnosis depends more upon the history of the symptomatology.

Frequently, x-ray studies with barium meal or enema are of much value. Meckel's diverticula and polyps are not detected by x-ray. Double contrast technique of insufflating the colon with air after the expulsion of barium increases the chances of detecting a polyp in the colon. On rare occasions when an adequate diagnostic study fails to reveal the cause of melena, laparotomy may be most valuable as a diagnostic acid and frequently is the curative measure.

GALACTOSEMIA

A Case Report with a Review of the Literature

*Case Report No. 246**

Joseph M. LoPresti, M.D.
Assia Itani, M.D.
E. Clarence Rice, M.D.

INTRODUCTION

The following case report is important because it illustrates that the presence of a copper-reducing substance in the urine of an infant must not be assumed to be glucose. Indeed, at a recent medical meeting, Jackson[1] suggested that galactosemia is a more common disorder in infancy than is diabetes mellitus. The increasing number of case reports of glactosemia in the medical literature is incontrovertible testimony in support of this view. On the other hand, infantile diabetes is a rather rare pathological entity. *When a copper-reducing substance is found in the urine of an infant, it is more likely to be galactose than glucose.* Further laboratory procedures should be performed to determine the specific nature of the melituria.

* This patient was admitted to the private service of Dr. Edgar P. Copeland.

Case Report No. 42–419

A two-week old white male infant was admitted to The Children's Hospital for the first time on January 10, 1952 with the chief complaints of vomiting and poor weight gain. The infant was the product of a normal, uncomplicated pregnancy and cried spontaneously at birth. The birth weight was 7 pounds, 6 ounces. He was placed on an evaporated milk formula and sent home on the fifth neonatal day. Shortly thereafter, it was noted that the infant fed poorly and regurgitated his feedings frequently. The vomiting was non-projectile. Two days before hospitalization the infant became lethargic and the anterior fontanel was discovered to be bulging. During this first two weeks of life, the infant had not regained his birth weight. An older sibling is normal and the family history revealed a paternal grandfather who cannot tolerate milk.

The physical examination revealed an afebrile, well-developed but malnourished white male infant who possessed a good cry and did not appear to be acutely ill. The weight was 6 pounds, 7 ounces. The skin showed a moderate decrease of tissue turgor. The head circumference measured 36 centimeters, and the chest, 33 centimeters. The anterior fontanel was patent, tense, and slightly bulging. No other physical abnormalities were noted.

The laboratory findings revealed a hemoglobin of 11.5 grams; 4,900,000 erythrocytes per cubic millimeter; and 17,400 leukocytes of which 57 were polymorphonuclear cells and 43 were lymphocytes per 100 cells. There was a shift to the left of the Schilling index. The platelets were normal and the urinalysis revealed a 4 plus sugar (orange) and many granular casts. A White-Lee clotting time was normal, and a marked hypoprothrombinemia was present. A subdural puncture was normal and the spinal fluid was cloudy and xanthochromic. It contained 50 milligrams per cent of protein, 60 milligrams per cent of sugar and 118 leukocytes per cubic millimeter with a differential of 67 per cent polymorphonuclear cells and 33 per cent lymphocytes. An x-ray of the skull revealed a slight bulge of the anterior fontanel and separation of the cranial sutures.

Because of the leukocytosis and spinal fluid findings, the infant was treated with penicillin and chloramphenicol. He was given parenteral vitamin K, fluids, and transfusions of whole blood. During the hospital stay, he was noted to feed poorly and regurgitated frequently. The evaporated milk formula was changed to a protein milk formula. Feeding improved, but vomiting continued. A re-examination of the spinal fluid six days after admission showed a protein content of 132 milligrams per 100 milliliters; sugar, 45; and a decrease in leukocytes to 36 per cubic millimeter. He was discharged ten days after hospitalization with a final diagnosis of intracranial hemorrhage. The infant had gained 6 ounces in weight.

At the age of one month, the patient was readmitted to the hospital for one day for a blood transfusion. At this time, the infant's weight was 7 pounds, 3 ounces. The patient was feeding well. A spinal fluid examination showed a pressure of 552 millimeters of water; the protein was 52 milligrams per cent; sugar, 120; and the leukocytes numbered less than 1 per cubic millimeter.

At the age of 3 months, the infant was admitted to the hospital for the third time. Although he had been taking his formula well, his weight gain had been poor (1 pound, 2 ounces in two months). He had become progressively pale and jaundice had appeared. At this time, the physical examination revealed an underdeveloped, malnourished white male infant who weighed 8 pounds, 3 ounces. The skin and conjunctivae were icteric and tissue turgor was poor. The infant was not able to follow light, to grasp objects, or to hold his head up. The head and chest circumferences were 41

and 37 centimeters respectively. The anterior fontanel was noted to be bulging. The abdomen was distended and covered with a collateral venous pattern. The liver was palpable 7 centimeters below the right intercostal margin, and a mild splenomegaly was present. An extensive laboratory work-up ensued:

1. The hemogram revealed 9.6 grams of hemoglobin; 2,900,000 eyrthrocytes, 14,000 leukocytes with a differential of 87 lymphocytes and 13 polymorphonuclear cells per 100 cells. There were 2 nucleated red blood cells per cubic milliliter and numerous target cells. Anisocytosis and macrocytosis were present.

2. Repeated urinalyses showed an orange reduction of Benedict's solution, albuminuria, and abundant granular casts. At no time was acetone or diacetic acid encountered. The blood urea nitrogen was 15.9 milligrams per 100 milliters and creatinine, 0.9.

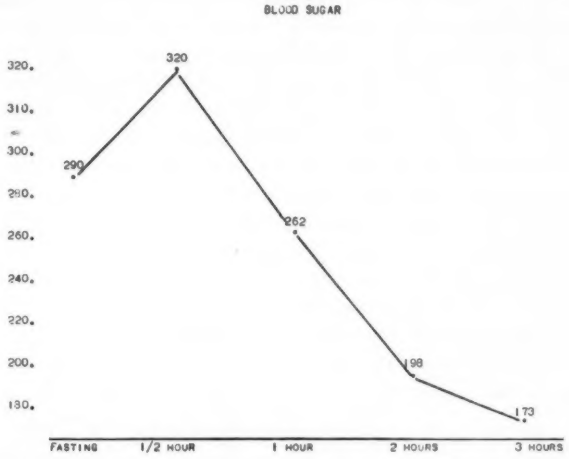

FIG. 1. Glucose tolerance curve. This is not typical of a diabetic curve

3. Liver function tests: the cephalin flocculation was 3 plus in 48 hours; the icteric index was 75; the total serum bilirubin, 2.80 milligrams per cent of which 1.15 was prompt and direct and 1.65 was indirect. Total protein was 5.95 grams per 100 cubic milliliters with an albumin to globulin ratio of 2.2; and a moderate hypoprothrombinemia was present.

4. The serum chlorides were 711 milligrams per 100 milliliters and the carbon dioxide combining power was 33 volumes per cent.

5. A ventriculogram revealed no abnormalities.

6. Daily fasting blood sugars ranged between 160–255 milligrams per 100 milliliters.

On the eighth hospital day, NPH insulin in a daily dosage of one unit given before the morning feeding was instituted. This was increased to 2 units on the tenth day of hospitalization. Despite this, the urinary sugar continued to produce an orange reaction with Benedict's solution. In this interim, bronchopneumonia developed and the patient responded to chloramphenicol. Thirteen days after admission, the infant

appeared to be hungrier than usual. A blood sugar at this time showed 255 milligrams per 100 milliliters. Shortly thereafter, the patient developed a clinical picture similar to insulin shock. The respirations were irregular; pulse, rapid, and the patient was comatose. He responded to coramine, adrenalin, and oxygen therapy. A diagnosis of galactosemia then was entertained. An ophthalmologist recorded abnormal eye findings interpreted as very early cataract formation. The urine was negative for pentose, lactose, and fructose; however, the mucin test for galactose was positive. A glucose tolerance curve was determined (Fig. 1) but was not typical of a diabetic curve. However, a galactose tolerance curve showed an early and sustained rise (Fig. 2).

Following these determinations, the patient was placed on a soy-bean formula, later this was changed to casein hydrolysate because of diarrhea. The response was

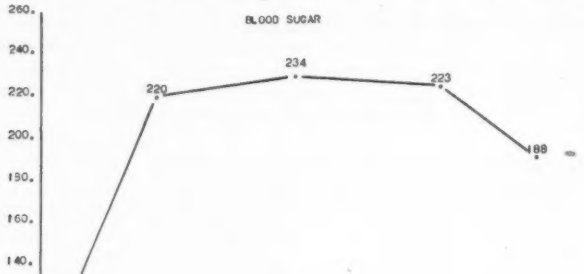

FIG. 2. Galactose tolerance test. The solid line represents non-fermentable sugar (galactose), and the dotted line represents fermentable sugar (glucose).

dramatic. In twenty-four hours the urine showed a negative reaction with Benedict's solution. The fasting capillary blood sugar dropped to 55 milligrams per 100 milliliters. In the remaining nine-day period of hospitalization, a weight gain of 13 ounces was achieved. The hepatomegaly decreased progressively; the abdomen became less distended, and the collateral circulation disappeared. The cephalin flocculation test was 2 plus in forty-eight hours, the total serum bilirubin had decreased to 0.36 milligrams per 100 milliliters of which 0.00 was indirect, and the carbon dioxide combining power had increased to 44 volumes per cent. At the present writing, the infant weighs 15 pounds and no evidence of physical or mental retardation is present.

DISCUSSION

Galactosemia is an uncommon disorder of carbohydrate metabolism characterized by the presence of significant and chemically identifiable

levels of galactose in the circulating blood, an inability of the body to utilize ingested galactose, and by galactosuria. It occurs almost exclusively in infants and has been referred to as galactose diabetes, galactemia, chronic hypergalactosemia, and chronic galactosemia.

Physiology

Galactose is an aldohexose seldom found free in nature but in combination it occurs both in animals and in plants. In the animal, this monosaccharide is a constituent of the glycolipids which are widespread but occur especially in nervous tissue. In combination with glucose by beta linkage, galactose forms lactose, the sugar found in milk.

In the small intestine, lactose is hydrolysed by the enzymatic action of lactase into its constituent monosaccharides. The latter are combined with phosphoric acid and are readily absorbed. The rate of absorption of the monosaccharides from the small intestine is different for each, e.g., galactose is the most rapidly absorbed, followed in decreasing order by glucose, fructose, mannose, and the pentoses. Galactose (phosphorylated) is then carried to the liver in the portal circulation. There it is converted to glycogen by the hepatic cells. This fact has been utilized as a test of hepatocellular function in the galactose tolerance test. It is important to note that when glycogen is broken down (glycogenolysis), it always yields glucose regardless of the hexoses which originally composed it. It is then apparent that galactosemia is not the result of the breakdown of glycogen. There is no renal threshold for galactose[2] and when 50 grams are given orally to normal patients, the maximum blood level is attained in one hour and no galactose is detectable at the end of two hours.

On oxidation, galactose yields relatively insoluble mucic acid, and the crystals may be detected readily under the microscope. The osazone of galactose also forms characteristic crystals which may likewise be identified. As a positive aid in identification, galactosazone has a specific melting point of 193 degrees centigrade. In addition, galactose is a non-fermentable sugar.

History

Galactosemia was first reported by von Reuss[3] in 1908 and the next case by Goppert[4] in 1917. The first case in the American literature was recorded by Mason and Turner[5] in 1935. Since then, two other cases have appeared in the German literature and 21 cases in English. At the present time, the total number of recorded cases, including this case report, is 27[3–19]. The most recent case was presented by Edmonds et al.[6] Over half of these cases have appeared in the past two years, a tribute to the skill of the modern clinician. The disease is probably more common than the literature would indicate, because in almost all large pediatric centers, unrecorded cases have been seen.

Etiology

Galactosemia is placed in the category of inborn errors of metabolism. It may be presumed that the defect lies in the complex enzymatic reactions which convert galactose to glycogen. A familial tendency, inferred or definite, has been noted in the siblings of 9 or 33.3 per cent of the recorded patients. The disease is almost entirely limited to infants and, in over 90 per cent, it has occurred under one year of age. The oldest patient was reported by Fanconi[7], a nine year old white male with concomitant neurofibromatosis. The male to female ratio is 16 to 11, an insignificant difference.

Pathology

Lamellar cataracts are found in some cases (12 or 44.4 per cent). The chief seat of the basic defect is, most probably, the liver, but not all galactose metabolism occurs in the liver. However, the liver is the main organ in the body to suffer anatomic damage. Blood chemical changes indicate hepatic pathology; but with appropriate therapy, liver damage appears to be reversible. Bell et al.[8] show that liver changes consist mainly of fatty infiltration similar to that found in diabetes and alcoholism; areas of focal necrosis are demonstrable. Townsend et al.[9] demonstrated classical Laennec's cirrhosis in 2 cases.

Pathologic Physiology

Greenman and Rathbun[10] found that glucose improved the utilization of galactose in their patient pointing to an interrelationship of the metabolism of these two monosaccharides. Therapeutic implications were made from their findings. These investigators feel that a high carbohydrate diet together with a restriction of galactose intake is indicated and beneficial in patients with galactosemia.

Bell et al.[8] feel that the fatty infiltration rather than glycogen storage is responsible for both liver dysfunction and hepatomegaly. They suggest that excessive fat in the hepatic cells may accentuate the congenital inability of the liver to metabolize galactose normally.

Melinkoff et al.[11] postulate that galactose itself is stored in the liver and is directly injurious to it. Proteinuria may be due to a similar process in the kidney or to the production of an abnormal plasma protein. In their case proteinuria was accompanied by a normal Addis count and a normal serum creatinine suggesting the production of an abnormal protein.

Mason and Turner[5] feel that the cause of the symptoms in galactosemia, in addition to the toxic effects of the elevated blood galactose, is the secondary low blood glucose. They suggest that the defect is probably in the enzyme system of the liver which converts galactose to glycogen. Be-

cause of this, galactose passes through the liver unchanged and enters the systemic circulation. This will raise the total blood sugar to an abnormal level and since the body is unable to remove galactose from the blood, it removes glucose which reaches abnormally low levels. Insulin causes a depression of the blood glucose levels regardless of the presence of galactose. The subcutaneous injection of adrenalin causes a rise in blood glucose whether or not galactose is present. Bruck and Rapoport[12] dispute this by noting that hyperinsulinism and glycogen storage disease are associated with low glucose levels but do not cause the same clinical symptoms; they feel that hypoglucosemia plays no role in the production of the clinical features.

Goldbloom et al.[13] report the infallible production of cataracts in animals by appreciably elevating galactose blood levels, inferring that galactose is the causative agent in humans. The objection is that the cataracts described are nuclear in type. In humans, nuclear cataracts generally are considered to form in the third fetal month before the development of the lens nucleus is completed.

A combination of factors is probably the cause of the pathological and clinical features of galactosemia:

1. A basic congenital defect in the complex enzyme system for converting galactose to glycogen.
2. A directly injurious effect on body tissues by the high galactose levels in the blood.
3. The secondary low blood glucose levels.

Further studies are necessary to determine the exact nature of the pathologic physiology.

The marked anemia is probably due to a combination of liver disease, malnutrition, and the toxic effect of galactose on the bone marrow.

Symptomatology

Table 1 lists the outstanding signs and symptoms of galactosemia. The clinical features are not apparent at birth but physiologic jaundice is often prolonged. The history of the disease in a sibling may be elicited. The infant develops normally for variable periods of time except for feeding difficulties which gradually become more severe. The most common finding and outstanding symptom which brings the patient to the physician's attention is the failure to gain weight on various milk formulae. In fact, the majority of cases have a history of many formula changes, and do not do well on any which contain whole milk. Vomiting occurs and even diarrhea may supervene. There is a failure to gain and weight loss with malnutrition and abdominal distension ensues. In some instances lamellar cataracts develop. Hepatomegaly is the most common physical finding and accounts for the

enlargement of the abdomen. Splenomegaly and ascites may occur and in some cases a visible venous collateral circulation will be found on the abdomen. The skin, sclerae, and mucous membranes may become icteric. Mental retardation develops invariably and is a salient complication. The development of marked anemia results in progressive pallor, weakness, and listlessness. Untreated cases run progressively downhill and die of malnutrition.

TABLE 1

A compilation of the more common symptoms and signs of galactosemia in the 27 cases reviewed

SYMPTOM OR SIGN	NUMBER	PER CENT
Melituria	26	96.3
Hepatomegaly	24	88.8
Albuminuria	23	85.1
Splenomegaly	15	55.5
Cataracts	12	44.4
Jaundice	12	44.4
Familial tendency	9	33.3
Ascites	6	22.2

Laboratory Findings

There is a copper-reducing substance in the urine which on osazone, mucin, and optical rotation tests proves to be galactose, a non-fermentable monosaccharide. *Albuminuria is invariably present and acetone is absent.* There is an abnormal galactose tolerance test. If a test dose of 0.5 to 1.75 grams of galactose per kilogram of body weight is administered intravenously, 25 per cent will be recovered in the urine. A low or normal blood glucose will be found, and a flat or normal glucose tolerance curve will be demonstrated. Hypoproteinemia may be found. Abnormal liver function tests are encountered frequently, e.g., prolonged prothrombin time, positive cephalin flocculation test, elevated thymol turbidity, elevated serum bilirubin, etc. There is a normal blood sugar response to adrenalin. Most of the patients develop a marked anemia, normocytic and hypochromic in type. The long bones may show a generalized osteoporosis.

Differential Diagnosis

Galactosemia should be considered in any infant who fails to develop normally and has significant enlargement of the liver. The finding of a copper-reducing substance in the urine of such a patient together with albuminuria and the absence of ketonuria strongly suggests the diagnosis. The identification of the reducing substance as galactose clinches the diagnosis.

1. Glycogen storage disease with liver involvement results in hepatomegaly due to an excessive deposition of glycogen. There is a defect in glycogenolysis, hypoglycemia, growth retardation, weakness, dyspnea, bleeding, susceptibility to infection, hepatomegaly, and occasionally convulsions. The laboratory findings include a fasting hypoglycemia, ketosis and acetonuria without glycosuria, minimal rise in blood sugar with the adrenalin tolerance test, and the results of the galactose and levulose tolerance tests are normal.

2. Gaucher's disease produces gradual hepatic enlargement, but the liver does not attain the size of the spleen which assumes tremendously large proportions.

3. Cirrhosis of the liver results in hepatomegaly associated with jaundice and evidence of disturbed liver function. Liver biopsy will establish the diagnosis.

4. Leukemia and megaloblastic anemia are differentiated by an examination of the blood and bone marrow.

5. Mucoviscidosis and celiac disease are differentiated by an examination of the stool and duodenal contents. In these entities, there is no melituria.

Course and Prognosis

Death ensues if the disease is untreated. However, the prognosis for life is excellent if the disease is diagnosed early and treated properly. Mental retardation is a common complication of the disorder. The hepatic dysfunction and lamellar cataracts appear to be reversible for the most part. Townsend et al.[9] reported a follow-up on a patient who is now 18 years old. The I.Q. is 84; liver function tests were normal, and the patient could tolerate galactose. This indicates that the disease is chronic but with advancing years there is no demonstrable evidence of somatic damage. These patients may gradually tolerate a normal diet without apparent toxic effects.

Treatment

Early recognition of the disease and identification of galactose as the cause of melituria are mandatory if treatment is to be effective. Therapy centers about *the elimination of all milk and milk products from the diet.* The elimination of galactose results in a prompt subsidence of the symptoms and a gradual return of the infant to normal. A soy-bean or casein hydrolysate formula will serve as milk substitutes. It is probable that a high glucose intake is indicated and beneficial. The cataracts which sometimes occur, if they do not disappear on a galactose-free diet after a fair trial, should be

treated by lens evacuation. This was necessary only once in the series reported.

SUMMARY

A case report of galactosemia in a white male infant has been presented together with a review of the literature. A total of 27 recorded cases were located. The history, etiology, pathology, pathologic physiology, symptomatology, laboratory findings, diagnosis, prognosis, and treatment of galactosemia in infancy have been summarized.

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